

DETAILED ACTION

Election/Restrictions

1. Claims 25-27, 30-26, and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 20 August 2010.

Claim Rejections - 35 USC § 102

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claims 1-3, 6-9, 12, 16, 17, and 19-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Langer et al.
4. Regarding Claims 1 and 2, Langer's examples teach biocompatible and biodegradable multiblock copolymers composed of a crystallizable hard segment and a soft segment (equivalent to the claimed pre-polymers) having a thermal transition temperature between room and body temperatures (col. 13, lines 35-40).
5. The hard segment consists of a polymer (PDS) prepared by reacting the cyclic monomer p-dioxane-2-one with ethylene glycol as a difunctional initiator (col. 13, lines 59-66).

6. Two soft segments are employed in various examples. The first is a poly(ϵ -caprolactone) diol (PCL) (col. 14, lines 9-11). The second is a polymer (PLCG) prepared by reacting a mixture of the cyclic monomers L,L-dilactide and diglycolide with ethylene glycol as a difunctional initiator (col. 14, lines 15-22).
7. Multiblock copolymers are prepared by reacting a mixture of one hard segment and one soft segment with trimethylhexane-1,6-diisocyanate (equivalent to the claimed multi-functional chain extender) while heating over a period of 10 days (col. 14, lines 45-53). No measures are taken to ensure any sort of sequential or patterned block polymerization; thus, the hard and soft segments will be connected randomly.
8. Multiblock copolymers having the following compositions and physical properties are formed (col. 15-16, Tables 3 and 5):

Composition and Transition Temperatures T_m and T_g of the Copolyester Urethanes							
Label	Hard Segment	Weight Content [%]*	Soft Segment	Weight Content [%]*	T_{m1} [° C.]	T_g [° C.]	T_{m2} [° C.]
PDL23	PDS	23.0	PLGA	54.2	—	34.5	—
PDL30	PDS	30.0	PLGA	52.1	—	33.5	85.0
PDC22	PDS	22.0	PCL	64.5	35.0	—	—
PDC27	PDS	27.0	PCL	61.1	37.0	—	75.5
PDC31	PDS	31.1	PCL	55.4	36.5	—	76.5
PDC40	PDS	40.4	PCL	46.2	35.0	—	77.5

*The difference to 100% is the urethane content.

9. PDL23 and PDL30 possess T_g values below 37°C, and will therefore be amorphous under physiological conditions. T_g was not measured for copolymers

PDC22, PDC27, PDC31, and PDC40. However, the Fox equation (Sheet 1) can be used to calculate a T_g value for PDC22, PDC27, PDC31, and PDC40.

10. The Fox equation is as follows:

$$\frac{1}{T_g} = \frac{w_a}{T_{g,a}} + \frac{w_b}{T_{g,b}}$$

wherein

T_g = glass transition of the copolymer;

w_a = weight fraction of component 'a';

w_b = weight fraction of component 'b';

T_{g,a} = T_g of component a; and

T_{g,b} = T_g of component b.

Table 1 (col. 14) illustrates the glass transition temperatures of each prepolymer segment:

<u>Molecular Weight and Thermal Properties of the Macrodiols</u>						
Label	M _n GPC [g · mol ⁻¹]	M _n VPO [g · mol ⁻¹]	T _m [° C.]	ΔH [J · g ⁻¹]	T _g [° C.]	ΔC _p [J · g ⁻¹]
PCL2000	1980	1690	43	73.5	<-40	—
PDS1300	1540	1340	97	74.5	<-20	—
PDS1200	2880	1230	95	75.0	<-20	—
PLGA2000	2020	1960	—	—	29.0	0.62

11. Using the T_g values from Table 1 and the composition data from Table 3 in the Fox equation, the T_g values of PDC22, PDC27, PDC31, and PDC40 are calculated to be -31.9°C, -30.6°C, -29.4°C, and -27.3°C, respectively. Each of the multiblock copolymers presented in Langer's examples exhibits a T_g below 37°C, and will

therefore be amorphous under physiological conditions. All of Langer's examples therefore anticipate Claims 1 and 2.

12. Regarding Claims 3 and 6, all of Langer's hard and soft segments contain ester linkages and residues of hydroxycarboxylic acids.

13. Regarding Claims 7 and 12, Langer's PDS and PLGA segments are reaction products of cyclic monomers and ethylene glycol.

14. Regarding Claims 8 and 9, PDS is derived from 1,4-dioxane-2-one. PCL is derived from ϵ -caprolactone. PLGA is derived from a mixture of lactide and glycolide.

15. Regarding Claims 16 and 19, as per Table 1 in paragraph 23 above, all prepolymer (macrodiol) segments have a number average molecular weight M_n between 1230 and 2880.

16. Regarding Claim 17, Langer's soft segments are comparable to the claimed prepolymer B. As set forth above, said soft segments comprise either ϵ -caprolactone or a mixture of lactide and glycolide.

17. Regarding Claim 20, as per the table presented in paragraph 21 above, Langer's soft segments are present in amounts ranging from 46.2 to 64.5 wt%.

Regarding Claim 21, Langer does not measure the intrinsic viscosity of said multiblock copolymers. However, said multiblock copolymers are chemically identical to the claimed copolymers, possess similar molecular weight, and are composed of prepolymers in similar weight percents. The courts have held that "a compound and all its properties are mutually inseparable", *In re Papesch*, 315F.2d 381, 137 USPQ 42, 51 (CCPA 1963). Further, attention is drawn to MPEP 2112.01, which states that "products

of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.", *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, although not measured by Langer, said copolymers will inherently possess the claimed intrinsic viscosity.

18. Regarding Claims 22 and 23, as set forth above, Langer's examples utilize trimethylhexane-1,6-diisocyanate (an aliphatic diisocyanate).

Claim Rejections - 35 USC § 103

19. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

20. Claims 4, 5, 10, 11, 13, 14, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Langer et al. Sheet 2 (Lactide pricing information, Alfa Aesar) is provided as extrinsic evidence.

21. In addressing Claims 4, 5, 10, 11, 13, 14, and 18, Langer remains as applied to Claim 1 above. Langer's specific embodiments do not satisfy all limitations of these claims. However, embodiments which read on the claims are contemplated within Langer's disclosure. It is understood that the modifications set forth below are to be

applied to the specific embodiments addressed in Langer's examples and applied in the rejection of Claim 1 above. It is further understood that any affect on the physical properties of the resulting modified copolymers will be minimal. One of ordinary skill in the art would have a reasonable expectation that the modified copolymers would possess Tg values similar to those of Langer's examples, and would therefore remain amorphous under physiological conditions.

22. Regarding Claim 4, representative synthetic polymer blocks suitable for use in Langer's copolymers include polyalkylene glycols and polyalkylene oxides (i.e. polyethers) (col. 6, line 67 – col. 7, line 1).

23. Regarding Claim 5, said polyalkylene glycols and polyalkylene oxides are taught as being suitable for the same purpose as the segments included in Langer's examples. It would have been obvious to one of ordinary skill in the art at the time of the invention to combine polyether segments and the exemplary polyester segments, as they are considered to be equivalents known for the same purpose. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

24. Regarding Claim 10, representative synthetic degradable polymer segments include poly[glycolide-co-(ε-caprolactone)] (col. 7, line 28). A preferred weight ratio of

the monomers is not disclosed; however, a 1:1 weight ratio is obvious without further guidance.

25. Regarding Claim 11, representative bioerodible polymer segments include poly(lactide-co-glycolide) (col. 7, lines 37-38). A preferred weight ratio of the monomers is not disclosed; however, a 1:1 weight ratio is obvious without further guidance.

26. Regarding Claims 13 and 14, suitable soft segments include polyethylene glycol (PEG) (col. 8, line 1) as well as poly(ethylene oxide-co-propylene oxide) (PEO-co-PPO; comparable to PEG-PPG) (col. 8, lines 23-24).

27. Regarding Claim 18, Langer's examples utilize L,L-lactide rather than the claimed D,L-lactide (i.e. racemic lactide). However, it is well known in the art that racemic reactants are generally lower in price than their enantiomerically pure counterparts. Although not necessary to the rejection, this is supported by Sheet 1, which indicates that the cost per 5g of racemic lactide is \$12.30, while the cost per 5g of L-lactide is \$18.20. Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to replace L,L-lactide with D,L-lactide in order to reduce cost.

28. Claims 4 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Langer as applied to claim 1 above, and further in view of Rashkov et al (Macromolecules, 1996, p. 50-56).

29. Regarding Claims 4 and 13-15, Langer remains as applied to Claim 1 above. Langer teaches that both polyethylene glycol (PEG) (col. 8, line 1) and polylactide (col.

7, line 24) are suitable polymer segments. Langer does not teach a copolymer wherein PEG is an initiator for ring-opening polymerization.

30. In the same field of endeavor, Rashkov teaches that PLA/PEG copolymers are of great interest as macromonomers for preparation of new macromolecular materials. Copolymerization offers the possibility of varying hydrophilic/hydrophobic and soft/hard segment ratios and, thus, constitutes a very attractive means to modulate the basic properties of each homopolymer (p. 50, Introduction, para. 1). Said PLA/PEG copolymers are synthesized by introducing PEG having a molecular weight of 600, 1000, or 2000 (p. 50, Materials) to a flask, followed by introduction of lactide (a cyclic monomer) and a catalyst (p. 50-51, Methods). The result is a copolymeric macromonomer formed by using PEG having a molecular weight of 600, 1000, or 2000 as an initiator for ring-opening polymerization of L-lactide.

31. It would have been obvious to one of ordinary skill in the art to employ Rashkov's PEG/PLA copolymers as segments in Langer's multiblock copolymers for the benefit of modulating the physical properties of the individual segments and because they are directly taught as being suitable for use as macromonomers for preparation of macromolecular materials. Modification of Langer in view of Rashkov reads on Claims 4 and 13-15.

Response to Arguments

32. Applicant's arguments filed 20 August 2010 have been fully considered but they are not persuasive.

33. The Applicant argues that Langer's copolymers are not amorphous under physiological conditions. Rather, the Applicant argues that Langer's copolymers are semi-crystalline, because they comprise the semi-crystalline p-dioxanone segments that have a melting temperature T_m above body temperature. The Applicant states that the melting temperature is preserved in the block copolymer, as is shown in Table 5 of Langer et al, for polymers PDL30, PDC27, PDC31, and PDC40.

34. First, it is noted that the claims do not require the multi-block copolymer to be wholly amorphous at physiological conditions, nor do they specify any degree to which the polymer must be amorphous. A polymer which comprises both crystalline and amorphous blocks will necessarily possess some domains which remain amorphous.

35. Langer's copolymers PDL23 and PDL30 possess a T_g (glass transition) of 34.5 or 33.5°C, respectively. T_g is generally known to be the temperature at which an amorphous region of a partially crystalline polymer changes from a hard and brittle state to a viscous or rubbery state. The fact that the T_g of these two polymers occurs below 37.1°C indicates that they will possess amorphous regions at body temperature.

36. Langer's polymer PDC22 possesses a T_m (melting temperature) of 35°C, and possesses no T_g or second T_m . Thus, this polymer will be wholly melted (i.e. amorphous) at body temperature.

37. The Applicant argues that the Fox equation relied upon by the Examiner to calculate Tg values of the remaining polymers in Table 5 is inapplicable when the copolymer comprises a semi-crystalline segment, and requires perfect mixing.

38. The Applicant has provided no evidence in support of this assertion. There are numerous examples in the art in which the Fox equation is used to calculate Tg for systems which include semicrystalline polymers. Examples will be provided at the Applicant's request. It is generally known that the Fox equation is not 100% accurate in calculating actual experimental Tg values, but does provide a reasonably accurate calculated value. The calculated Tg values of the polymers in question range from -27.3°C to -31.9°C. Thus, in order for these polymers to possess a Tg above body temperature, the calculated values must be off by anywhere from 64.4 °C to 69.0 °C. Given the widely established use of the Fox equation in the art, the lack of evidence presented by the Applicant, and the large margin of error required to place the polymers in question outside the scope of the instant claims, this line of argument is not convincing.

39. The Applicant argues that although Langer's Table 5 shows that PDL23 and PDC22 do not have a defined melting temperature, the polymers are nevertheless inherently crystalline because they are shape-memory polymers. The Applicant points to column 3, lines 7-10, which states that the phase transition of the hard segment is at least 10°C higher than the soft segment, as evidence of crystallinity.

40. The Applicant's arguments are in direct conflict with the evidence presented in Langer's Table 5. No evidence has been presented which would cause one of ordinary

skill in the art to question the veracity of Langer's experimental data. The Applicant further ignores the portion cited in evidence of crystallinity. Column 3, lines 7-10, does state that the phase transition of the hard segment is at least 10°C higher than the soft segment. However, it also states that the phase transition of the hard segment can occur at temperatures as low as -30°C, well below physiological temperature. The cited portion of Langer does not demonstrate that the hard segment of a copolymer is inherently crystalline at physiological temperature.

41. The Applicant argues that because Langer teaches that the T_{trans} for the soft segments is the T_m or T_g of the polymer which makes up the soft segment, the same must be true for the hard segment. The Applicant concludes that the T_{trans} of PDC22 and PDL23 must be 95°C. The Applicant presents additional arguments speculating why some examples in Langer's Table 5 list a T_m value.

42. The Applicant's argument again contradicts the experimental data presented in Langer's Table 5. There is no indication of any transition taking place at 95°C. Transitions are clearly observed at temperatures a few degrees above or below the T_{trans} of the soft segments. In PDL23 and PDC22, there is no other transition. Additionally, the Applicant's speculations regarding lack of observed T_m are not substantiated by any sort of evidence. Absent any evidence to the contrary, it is assumed that Langer's Table 5 is true and does not contain erroneous data nor omit any data.

43. In the remaining polymers, a second T_{trans} is observed corresponding to the hard segment. This indicates that there remains some degree of crystallinity in the hard

segments of Langer's copolymers at body temperature under dry conditions. However, as previously stated, the claims do not require a particular degree of amorphous character. It is without question that in these polymers, at least the soft segment will be in an amorphous state below body temperature. Thus, the polymers will be at least partially amorphous at physiological conditions, satisfying the claim limitation.

44. It is important to note that Langer's measurement of T_{trans} takes place in a dry state. When in a dry state, Langer's multi-block copolymers may have T_{trans} values that are higher than they would be under physiological conditions. Upon application in vivo, the dry material's T_{trans} will drop as a result of the absorption of water (see instant specification, p. 9, lines 9-22).

45. The instant specification further states that while the inventive polymers are amorphous at physiological conditions, they may be partly crystalline in the dry state (p. 9, lines 29-31). Thus, although Langer's copolymers may in fact possess partial crystallinity in the dry state, they may nevertheless be wholly amorphous under physiological conditions.

46. It is also important to note that the claims only specify that the multi-block copolymer "is amorphous at physiological (body) conditions." The specification defines human body conditions as being 37°C and a moist environment. However, the claim does not specify human body conditions. As per the specification, body temperature in other mammals may be higher than 37°C (see instant specification, p. 9, lines 23-28). Thus, even copolymers having a T_{trans} above 37°C may still fall within the bounds of a

copolymer which is amorphous at physiological conditions as defined by the specification.

47. It is further noted that dependent Claims 8 and 17 allow for a copolymer possessing a block based on ϵ -caprolactone and a block based on p-dioxanone. Langer's Table 5 illustrates four block copolymers possessing a poly(ϵ -caprolactone) block and a poly(p-dioxanone) block. These blocks are described by the instant specification as being suitable for forming the inventive copolymer. If it is the Applicant's position that Langer's copolymers do not, in fact, possess the requisite amorphous regions under physiological conditions, it would be the Office's position that the application contains inadequate disclosure in that there is no adequate teaching as to how to obtain a composition with these properties.
48. The Applicant argues that Langer's copolymers must have a T_{trans} of the hard segment under physiological conditions, to enable retainment of the memorized shape in the body.
49. Contrary to the Applicant's argument, Column 3, lines 7-10 states that the phase transition (T_{trans}) of the hard segment can occur at temperatures as low as -30°C , well below physiological temperature.
50. The Applicant refers to a publication by Langer and Lendlein as establishing that Langer's PDC copolymers are indeed semi-crystalline.
51. It is noted that a copy of this publication was not included with the Applicant's response. Nevertheless, although the copolymers presented in the publication do possess blocks which are similar to Langer's, the length of the blocks is not indicated.

Thus, there is no indication that Langer's copolymers will exhibit the same behavior and characteristics. Additionally, the measurements made in the publication are again conducted under dry conditions. As per the instant specification, copolymers may possess partial crystallinity in the dry state, but may nevertheless be wholly amorphous under physiological conditions (p. 9, lines 29-31).

52. The Applicant argues that one of ordinary skill in the art would not have been motivated to modify Langer as per the rejection under 35 USC 103(a) of Claims 4, 5, 10, 11, 13, 14, and 18, and would not have a reasonable expectation of success in carrying out this modification.

53. The "modification" of Langer applied to the rejection in question merely involves selecting materials taught as being suitable for forming copolymers from a list. It has been established that selection of a known material based on its suitability for its intended use is *prima facie* obvious (*Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)). "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." (325 U.S. at 335, 65 USPQ at 301.). See MPEP 2144.07. Additionally, one of ordinary skill in the art would have every expectation of success when selecting said materials, as they are already taught by Langer as being suitable for forming said copolymers.

54. With respect to the rejection of Claims 4 and 13-15 over Langer in view of Rashkov, the Applicant argues that the fundamental deficiencies in the Office's *prima facie* case of obviousness over Langer alone are not remedied by Rashkov.

55. The Applicant presents no arguments specifically directed to the combination of Langer and Rashkov, nor any arguments directed to Rashkov specifically. It is believed that the arguments regarding Langer have been sufficiently addressed above.

56. Absent any further arguments, evidence, or substantive amendment to the claims, all previously presented rejections are maintained.

Conclusion

57. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

58. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

59. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT JONES whose telephone number is (571)270-7733. The examiner can normally be reached on Monday - Thursday, 9 AM - 5 PM.

60. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Wu can be reached on 571-272-1114. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

61. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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